REMARKS

The Office Action mailed January 13, 2003 set an initial three (3) month period for response. Applicants note that submitted herewith is a Petition under 37 C.F.R. § 1.136(a) for a two-month extension of time and a check which includes the required fee. With the granting of this Petition, the time period in which to submit a timely response to the Office Action mailed January 13, 2003 will be extended to June 13, 2003.

The Pending Claims

Claims 1, 3, 14, 25, 26, 35 and 43 have been amended to more particularly point out and distinctly claim aspects of Applicants' invention. Claims 2 and 24 have been cancelled without prejudice to expedite prosecution. Applicants reserve their rights to pursue subject matter deleted from the amended claims and the subject matter of the cancelled claims in continuing and/or divisional applications, as appropriate.

Claim 1 has been amended to be directed to compounds where V is $-C(R_9)-$. See, e.g., the specification at page 38, line 26. In view of the amendment of claim 1, claims 2 and 24 have been cancelled. Claim 3, 14, 25, 26, 35 and 43, formerly dependent on either cancelled claims 2 or 24, have been amended to revise their dependency so that they are not dependent on a cancelled claim.

Applicants note the Examiner's comments on their traverse of the Examiners restriction requirement. Applicants note that even though they did not agree with the Examiner's position with respect to restriction, in order to expedite allowance of claims directed to their elected invention of Group II, in their amendment mailed October 30, 2002, Applicants amended the claims

to focus on elected Group II and to delete the subject matter of the non-elected Group I.

Accordingly, Applicants note that they need not deal further with issues related to the restriction requirement in connection with the present application.

New claims 57 and 58 have been added. Claim 57 is directed to pharmaceutical compositions comprising compounds of Applicants invention. Claim 58 is directed to methods of treatment comprising compounds of Applicant's invention. Applicants submit that the new claims are clearly supported by the specification and claims as originally filed and give rise to no issue of new matter. (see, e.g. Specification at pages 48 to 49.)

The Section 112, First Paragraph, Rejection of Pages 5 to 9

Claims 34 to 49 stand rejected under 35 U.S.C. §112, first paragraph, as assertedly nonenabled.

This rejection is respectfully traversed. Applicants note that the Examiner has maintained his rejection on these grounds. Applicants submit that the Examiner's position is not well taken and that claims 34 to 49 as presently pending, clearly comply with the first paragraph of Section 112.

Applicants reiterate their traverse as set forth in pages 4 to 8 of their Amendment under 37 C.F.R. §1.111 mailed October 30, 2002 which responded to the Office Action mailed May 30, 2002.

Applicants note that the claim language of pharmaceutical composition claims 34 to 41 and method of use claims 42 to 49 represents conventional language used in the art and that the meaning of the terms used is understood by those of skill in the art. See, e.g., United States Patent Nos. 6,506,754; 6,506,760;

6,506,761 and 6,541,467. Applicants submit that one of skill in the art would be able to practice the subject matter of claims 34 to 49 without undue experimentation.

In particular, Applicants note that the class of compounds used in the pharmaceutical compositions of claims 34 to 41 and whose use is claimed in claims 42 to 49 have been demonstrated to be selective inhibitors of thrombin. See Table I in the specification at page 83.

Applicants note that the compounds of Applicants' invention that act as inhibitors of thrombin have been proposed as therapeutic agents for the treatment of conditions characterized by abnormal thrombosis and in decreasing the incidence of conditions characterized by abnormal thrombosis. (Applicants note the Examiner's comments regarding "decrease the incidence" and note that the quoted term would be understood to indicate that the treatment would decrease the likelihood of such an event in an individual considered susceptible to having such a condition.)

Applicants note that conditions characterized by abnormal thrombosis include a number of disease states and pathologic conditions which are related to and associated with abnormal hemostasis. (See, e.g., the Specification at page 6, line 22 to page 8, line 16 and page 48, line 13 to page 49, line 9.)

With respect to the Examiner's comments regarding the assays described in the Specification, Applicants note that compounds of the present invention were demonstrated to be active as selective inhibitors of thrombin in the *in vitro* assays. Such activity in these assays is recognized by those of skill in the art as reasonably predictive of *in vivo* activity in treating and/or decreasing the incidence of conditions characterized by abnormal thrombosis. As Applicants have

previously noted in their Amendment mailed October 30, 2002, such assays are used by those of skill in the art to select compounds for further study in animal models of conditions characterized by abnormal thrombosis and in the possible selection of clinical trial candidates.

Compounds of the present invention are active as non-covalent inhibitors of thrombin.

Applicants note that the Examiner has cited two "Pub Med" abstracts, Rauch *et. al* (Rauch *et al.*, "Thrombus Formation on Atherscleroticc Plaques: Pathogenesis and Clinical Consequences," Ann. Internal Med., 2001 Feb 6, 134(3):225-38) and Van Aken *et al.* (Van Aken *et al.*, "Anticoagulation: The Present and Future," Clin. Appl Thromb. Hemost. 2001 Jul.; 7(3):195-204), which appear to be abstracts of journal articles in support of the present rejection.

Applicants have reviewed an online copy of the Rauch *et al.* article which was abstracted as the Rauch *et al.* abstract. (A copy of this article is submitted herewith.) Applicants note that the Rauch *et al.* article appears to be a review article which summarizes reports on certain therapies for cardiovascular disease. Applicants submit that the portion of the Rauch *et al.* abstract cited by the Examiner when read in the context of the article as a whole is a statement of the long felt need of new therapies (including factor Xa inhibitors) for treatment of cardiovascular disease. Applicants note that Rauch *et al.* teaches that therapies they describe as under development have promise (see page 8).

With respect to the Van Aken *et al.* abstract, Applicants have not been able to obtain a copy of the article upon which the Van Aken *et al.* abstract is based. Applicants submit that

the Van Aken *et al.* abstract teaches that direct non-covalent thrombin inhibitors have promise:

> The development of reversible non-covalent DTI's[1] such as inogatran and melagatran, has resulted in safer, more specific and predictable anticoagulant treatment. Oral DTI's, such as ximelagatran are set to provide a further breakthrough in the prophylaxis and treatment of thrombosis.

Applicants note that their compounds are non-covalent direct thrombin inhibitors. Accordingly, Applicants submit that Van Aken *et al.* clearly would suggest that DTI's may be effective in the treatment and prevention of conditions characterized by abnormal thrombosis.

Applicants request that the Examiner reconsider his rejection of claims 34 to 49 on these grounds and withdraw it.

Applicants note that new claims 57 and 58, directed to pharmaceutical compositions and methods of treatment, respectively, have been added. Applicants note that conditions characterized by abnormal thrombus formation are described in the Specification at, *inter alia*, pages 48 to 49. Applicants submit that these claims comply with the first paragraph of Section 112.

The Section 103 Rejection

Claims 1, 21 to 23, 34, 42 and 54 to 56 stand rejected under 35 U.S.C. § 103(a) as unpatentable over WO 97/01338 to Sanderon *et al.* ("Sanderson *et al.*").

This rejection is respectfully traversed.

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[1] DTI = direct thrombin inhibitors.

Claim 1 has been amended to incorporate the subject matter and limitations of claim 2. Applicants note that the Examiner has indicated that claim 2 was directed to allowable subject matter. Claims 21 to 23, 34, 42 and 54 to 56 are either dependent or ultimately dependent on claim 1. Accordingly, Applicants submit that claims 1, 21 to 23, 34, 42 and 54 to 56, as pending after entry of the present amendments, are clearly unobvious over Sanderson *et al.*

Applicants request that the Examiner reconsider the present rejection in view of their remarks and withdraw it.

Allowable Subject Matter

In the office action mailed January 13, 2003, the Examiner indicated that claims 2 to 20, 24 to 29, 33 and 50 to 53 were directed to allowable subject matter and would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph.

Applicants note that in a telephone conversation with the Examiner on June 5, 2003, the Examiner noted that claims 2 to 20, 24 to 29, 33 and 50 to 53 should have been objected to as dependent on a rejected base claim, since there was no outstanding Section 112, second paragraph, rejection to overcome.

Applicants note that the limitation of claim 2 has been incorporated into claim 1. In view of the amendment of claim 1, claims 2 and 24 have been cancelled (since both add the limitation that V is $-C(R_9)-$).

Accordingly, applicants submit that claims 1, 3 to 20, 25 to 29, 33 and 50 to 53 are allowable.

CONCLUSION

In view of the foregoing, Applicants submit that all the rejections of claims 1, 21 to 23, 34 to 49 and 54 to 56 have been overcome and that those claims are allowable. Applicants submit that claims 3 to 8, 10 to 12, 14, 15, 18 to 20, 24 to 29, 33 and 50 to 53 are allowable as well. Applicants submit that new claims 57 and 58 are allowable. Applicants request that the claims be allowed and passed to issue.

If the Examiner believes that a telephonic interview would expedite allowance of this application, he is encouraged to telephone Applicants attorney of record, Suzanne L. Biggs at the below-noted telephone number.

The Commissioner is hereby authorized to charge any fee, including any fee due with this submission, if the attached check(s) is in the wrong amount or otherwise improper or missing, that may be due in connection with this and the attached papers, or with this application during its entire pendency to or to credit any overpayment to Deposit Account 03-3975, Order No. 018813-0272492.

Respectfully submitted,
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